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Analysis of repeated proton beam therapy for patients with hepatocelular carcinoma

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Purpose/Objective: Hepatocellular carcinoma (HCC) is multi-centric disease, and most of the patients suffer from recurrence. In general, tolerance dose of the liver is not very high, therefore, stereotactic radiotherapy for small tumor (<= 5 cm) is popular strategy of photon radiotherapy. In contrast, we have conducted definitive proton beam therapy (PBT) for many patients even with large HCC. And some of the patients received PBT repeatedly because of the recurrence. The purpose of this study is to analyze the course of repeated PBT for liver HCC, and evaluated its safety and efficacy.

Materials and Methods: Patients who received multiple course of definitive PBT (>= 50 GyE) for liver HCC from 2002 to 2012 were retrospectively analyzed. Proton beams were delivered with respiratory gating. Eighty-eight patients received PBT for 2-4 courses of PBT. The patients group included 70 male and 18 female, and the median age of the patients was 69 years old (range: 46 – 86). Eleven and 63 patients were infected by hepatitis-B and hepatitis-C virus, respectively, and 14 patients were not infected with hepatitis virus.

Results: The number of treatment course was 2, 3, 4 for 66, 18, 4 patients, respectively. The median planned total doses was 70.0 GyE for all tumors of all patients, and the median dose for 1st, 2nd, 3rd and 4th treatment was 70.0, 71.3, 71.3, and 69.3 GyE, respectively. The median CTV was 28.5 cc (2.8 - 936.2 cc) for of all treatment of all the patients, and 34, 25, 14, 36 cc for the 1st, 2nd, 3rd and 4th treatment. Fifty-nine patients received PBT for completely different tumors outside of the previous treatment fields, but 22 and 7 patients received PBT for the recurrent tumor within the previous fields and for the marginal recurrent tumor. The median follow up period from the start of the first PBT was 45 months, and the median overall survival from the first PBT was 61 months for all patients (95% CI: 52 - 70 months). Severe acute and chronic toxicity was not observed. Eight patients were dead of hepatic failure, but all of which were induced by disease progression. Serious radiation induced liver disease was not observed.

Conclusions: Definitive repeated PBT for liver HCC is safe and effective.

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Radiation dose-dependent changes of the spleen following chemoradiotherapy for gastric cancer

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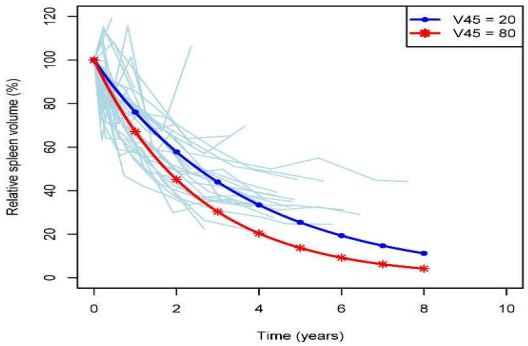
Purpose/Objective: The spleen often receives a high dose in chemoradiotherapy (CRT) for gastric cancer, due to its anatomical location and the fact that its hilar region is part of the CTV. Yet, the spleen is not considered as organ at risk, because it is largely unknown whether and to what extent the splenic function is affected by radiation (RT). However, histological changes of the spleen after irradiation, such as a decreased organ weight and white pulp depletion, have been described. Furthermore, following surgical splenectomy, patients are at an increased risk for fatal thromboembolic events and infections. The objective of this retrospective study was to investigate radiation-induced changes of the spleen after postoperative CRT for gastric cancer.

Materials and Methods: We included gastric cancer patients who received postoperative CRT, consisting of 45 Gy RT with concurrent capecitabine and cisplatin, in our institute between 2006-2011. The spleen was manually delineated on the RT-planning CT-scan to retrieve the dose-volume histogram, and on all diagnostic CT-scans at follow-up to calculate its volume (normal value 100-400 cc). Data on clinical adverse events, defined as pneumonia, fatal infection and thromboembolic event, were collected. Mixed effects and Cox regression models were used to evaluate radiation dose-dependent changes in spleen volume and clinical adverse events over time, considering age, comorbidity, chemotherapy, and surgery.

Results: Forty-six out of 99 consecutive patients were evaluable. All patients received 45 Gy in 25 fractions (concurrent capecitabine n=8, capecitabine/cisplatin n=38). Neoadjuvant chemotherapy (epirubicine, cisplatin, capecitabine) was administered in 50%. Median follow-up time from the end of treatment until the last visit or death was 66 (95% CI 56-76) months. Median (range) V10, V20, V30, V40 and V45 of the spleen were 100 (84-100), 99.9 (78-100), 91 (66-100), 60 (26-100) and 18 (3-93) % respectively, Dmean was 40 (32-46) Gy. Mean (95% CI) spleen volume decreased over time from 201 (173-234) cc to 82 (64-106) cc at 4 years ($p<0.001$), corresponding to a mean relative spleen volume of 33 (29-38) % (figure). This was only associated with the V40 ($p=0.003$), V45 ($p<0.001$) and Dmean ($p=0.013$). At follow-up, 13 patients had 19 clinical adverse events (pneumonia n=13, fatal infection n=2, thromboembolic n=4). Mean onset time from the end of treatment to the first clinical event was 65 (95% CI 54-76) months. The cumulative incidence increased in time. None of the tested factors were associated.

Figure.



Model-based dose-effect relationship of the V45 of the spleen (relative volume of the spleen that received 45 Gy) and relative spleen volume, depicted for two different V45 levels. The dark blue line with cirkels depicts the fitted curve for a V45 of 20%, and the dark red line with stars depicts the fitted curve for a V45 of 80%, the light blue lines are the individual patient curves.

Conclusions: Following CRT for gastric cancer, spleen volume decreased progressively and radiation-dose dependently to below normal, and to a third of its original size at 4 years. Thromboembolic and infectious events were observed in 28% of our patients. Although these events were not related to radiation dose, this study emphasises the need for prospective research on the consequences after irradiation of the spleen.

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Adjuvant three-dimensional radiotherapy after radical surgery may improve survival in T2-3N0M0 esophageal cancer

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Purpose/Objective: The prognosis of pathological T2-3N0M0 (pT2-3N0M0) thoracic esophageal squamous cell carcinoma (TESCC) after radical surgery is poor and neither adjuvant chemotherapy nor two-dimensional radiotherapy provided survival benefit. However, the distinct dosimetric advantages of three-dimensional radiotherapy (3DRT) techniques, such as intensity-modulated radiotherapy or three-dimensional conformal radiotherapy, provide theoretical possibility of survival benefit. This study was designed to assess the clinical value of adjuvant 3DRT after radical surgery compared with surgery alone for pT2-3N0M0 TESCC.

Materials and Methods: We compared the overall survival (OS) , disease free survival (DFS) and recurrences of the 96 consecutive patients receiving adjuvant 3DRT after surgery (S+3DRT) from 2004 to 2011 with that of 820 consecutive patients undergoing surgery alone (S alone) contemporaneously in our hospital as a control. The prescribed dose was 50-60 Gy to 95% of the planning target volume, encompassing the tumor bed and lymphatic drainage regions with high risk. Cox regression model was used to perform univariate and multivariate analyses of the effect of covariates on OS and DFS. Sensitivity analyses and propensity score-matched analyses were used for further confirmation.

Results: Group S+3DRT had more patients with tumor length ≥5cm and T3 stage than group S alone (P<0.05, both), while other characteristics were comparable. The median follow-up was 46.4 (3.1-127.2) months for the entire cohort and 60.3 (28.9-127.2) months for the surviving patients. The rate of 5-year OS and DFS for group S+3DRT versus group S alone was 74.3% versus 59.9% (P=0.010), and 71.0% versus 51.7% (P=0.003), respectively (Figure A1, A2). Multivariate Cox regression analyses revealed group S+3DRT was independently associated with an improved OS (Hazard ratio [HR] = 0.629, P=0.030) and DFS (HR=0.565, P=0.004) compared with group S alone (Table). Sensitivity analyses demonstrated that S+3DRT maintained its significance both in patients with number of nodes harvested ≥25 (P=0.025 for OS; P=0.046 for DFS) and in patients with DFS ≥9 months (P=0.041 for OS; and P=0.006 for DFS). Propensity score-matched analyses also comfirmed the improved 5-year OS (P=0.035) and DFS (P=0.025) in group S+3DRT versus group S alone (Figure B1, B2). The incidence rate of overall recurrence, locoregional recurrence and distant metastasis for group S+3DRT versus group S alone was 22.9% versus 43.0% (P<0.001), 18.8% versus 35.2% (P=0.001), and 11.5% versus 21.3% (P=0.024), respectively. No grade 4 to 5 radiation-related toxicities were observed in group S+3DRT, both early and late grade 3 toxicities developed in 25 patients (26.0%).

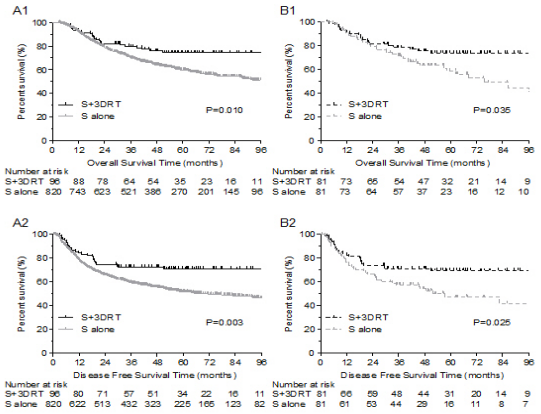

Table Multivariate Cox regression analysis for predictors of OS and DFS in the whole population

	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Age (continuous)	1.021(1.009-1.034)	0.001	-	-
Sex (Male vs. Female)	1.529(1.161-2.013)	0.002	1.535(1.192-1.976)	0.001
Location (Lower vs. Upper+Middle)	0.773(0.613-0.974)	0.029	0.641(0.517-0.794)	<0.001
Tumor length (≥ vs. < 5cm)	1.266(1.026-1.564)	0.028	-	-
Differentiation (G1+G2 vs. G3+G4)	1.395(1.097-1.773)	0.007	1.372(1.095-1.720)	0.006
Number of nodes harvested (continuous)	0.987(0.976-0.998)	0.022	0.990(0.980-1.000)	0.045
Proximal margin length (> vs. ≤5cm)	0.742(0.582-0.947)	0.016	-	-
Intravascular invasion (Yes vs. No)	1.782(1.160-2.738)	0.008	1.735(1.169-2.575)	0.006
3DRT (Yes vs. No)	0.629(0.414-0.956)	0.030	0.565(0.384-0.829)	0.004

OS: overall survival; DFS: disease free survival; HR: Hazard ratio; CI: confidence interval; 3DRT: three dimensional radiotherapy

Conclusions: Compared with surgery alone, adjuvant 3DRT reduces locoregional recurrences and distant metastases, resulting in improved DFS and OS with tolerable toxicities for pT2-3N0M0 TESCC.